Remarks

Claims 12 – 14 are currently pending. There are no new amendments presented herein. Applicant respectfully submits that the application is in condition for allowance for the reasons set forth below.

Double Patenting Rejections

Claims 12 – 14 have been rejected as being unpatentable over claims 1, 4 and 8 of US Patent No. 6,500,804. This rejection is respectfully traversed for the reasons that follow.

Claim 1 of US Patent No. 6,500,804 is directed to a method of increasing the capacity of insulin producing cells by administering a therapeutically effective dose of at least one DP IV enzyme activity effector. The present claims are directed to regeneration of insulin producing β -cells. The methods of the present invention provide long-lasting efficacy in the treatment of diseases such as diabetes by modifying the course of the disease. In particular, the therapeutic potential of DP IV inhibitors in diabetic subjects according to the present invention extends beyond glycemic control and increased capacity to produce insulin, to include increases in β -cell mass and function. Such a method resulting in an increase in β -cell mass over time alters the course of diabetes as a progressive disease. Applicants respectfully submit that the invention as presently claimed is patentably distinct from the claims of the '804 patent and request that the rejection in view of obviousness-type double patenting be withdrawn.

Claims 12 – 14 have been rejected as being unpatentable over claims 12 – 16 of copending Application Serial. No. 10/910,176. Applicants will submit a terminal disclaimer upon indication of allowance of the present claims.

Rejections Under 35 U.S.C. 102

Claims 12 - 14 have been rejected as allegedly being anticipated by Villhauer (US Patent No. 6,011,155). A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently described, in a single prior art reference.

Verdegaal Bros. V. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully submit that claim 12 is not anticipated by Villhauer because Villhauer does not disclose, either expressly or inherently, the regeneration of β -cells.

The present invention is directed to a method for the regeneration of β -cells in the pancreas of a mammal resulting in the stimulation of carbohydrate metabolism. A DP IV inhibitor is administered. By inhibiting the DP IV's enzymatic activity, the half-life of the active form of GLP-1 will be appreciably extended and maintained. (See, for example, column 4, lines 57-60). Prolonging the GLP-1's physiological active presence in the pancreatic tissue, facilitates the differentiation of pancreatic epithelial cells into new insulin producing β-cells. (See, for example, column 4, lines 60-64).

Villhauer is silent in regard to the novel method of claim 12 causing stimulation of carbohydrate metabolism through regeneration of β -cells in the pancreas. Villhauer administered a variety of DP IV inhibitors to treat conditions mediated by DPIV such as non-insulin dependent diabetes mellitus and other conditions of impaired glucose tolerance. (column 9, lines 48-65) It was found that the administration of the inhibitor improved the early insulin response to an oral glucose challenge through providing a dosage, one to three times a day (column 9, line 65 – column 10, line 42). The method therefore merely inhibits DP IV to acutely treat a condition in a patient in need of such treatment, but is prominently silent as to treating the patient by physiologically changing the patient by causing β -cell regeneration. Thus, the present invention is not anticipated by Villhauer since Villhauer is expressly silent as to causing regeneration of β -cells in the pancreas.

Furthermore, the element of causing cells present in the pancreas to differentiate into insulin producing cells is not inherent in Villhauer. "In order for a claim to be inherent in the prior art it is not sufficient that a person following the disclosure sometimes obtain the result set forth in the claim, it must invariably happen." *Glaxo Inc. v. Novopharm Ltd.*, 830 F. Supp. 871, 29 USPQ2d 1126 (E.D.N.C. 1993), *aff'd* 52 F.3d 1043, USPQ2d 1565 (Fed. Cir. 1995), *cert. denied 516 U.S. 998 (1995)* (citing Standard

Oil v. Montedison, 664 F.2d 356, 372 (3rd Cir. 1981). Villhauer fails to "invariably" obtain the result of regenerating β -cells.

Type 2 diabetes is characterized by an inexorable decline in insulin producing cell (β -cell) function with time. This phenomenon is demonstrated by data from the United Kingdom Prospective Diabetes Study, *Diabetes* 44:1249-1258, 1995; Figure 4.

There is no *a priori* reason to believe that therapies which chronically lower blood glucose concentrations by repeated acute dosing will lead to a reduction in the rate of decline of underlying β -cell function with time. Figure 4B demonstrates that treatment with metformin, which lowers blood glucose both acutely and chronically (through repeated dosing), results in the same rate of decline of β -cell function as that seen in patients treated with diet alone. Fig. 4A shows that treatment with sulphonylurea results in improved β-cell function, which leads to decreased glucose concentrations. However, sulphonylureas only improve β-cell function acutely. Over time, as seen in Fig. 4B, the β-cell function declines at the same rate as that of diet treated patients. Thus, treatments that do not cause cells present in the pancreas to differentiate into insulin producing cells will not preserve or restore β-cell function – which will inexorably decline as shown in the parallel curves on Fig. 4A and 4B.

Similarly Villhauer, suggests that the dosage be altered depending upon the patient to determine the optimal dosage and to avoid side effects. (column 10,lines 28-47). Therefore, the treatment is limited to administration of the inhibitor in response to the glucose challenge, not as a corrective mechanism of regeneration of the pancreatic insulin producing cells. Therefore, it does not invariably dose repeatedly and thus, will not invariably produce the effect seen here causing cells present in the pancreas to regenerate into insulin producing cells.

Efendic et al. (US Patent No. 5,631,224) further supports the lack of inherency of the presently claimed method. Column 1, lines 34-57 of Efendic et al. describes the use of sulfonylureas to treat Type II diabetes and indicates that in general, such treatment fails and patients will require insulin therapy. This failure in treatment is ascribed to

exhaustion of β -cells. Thus, as further evidenced in Efendic et al., acute treatment of elevated blood glucose levels does not inherently result in the regeneration of β -cells.

Applicants respectfully submit that claims 12 - 14 are not anticipated by Villhauer and request withdrawal of the rejection. Applicants respectfully request withdrawal of the rejections and request issuance of a Notice of Allowability.

The Commissioner is hereby authorized to charge any fees due in connection herewith to Deposit Account No. **50-2783**.

Respectfully submitted,

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